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To the commercial court
of the canton of Zurich
Hirschengraben 15
P.O. Box
8023 Zurich

November 23, 2001 STW/BLF/WUA

Mr. President,
Ladies and Gentlemen,

In re

F. Hoffmann-La Roche AG
Grenzacherstr. 124, 4058 Basel **"Plaintiff"**

represented by Dr. Werner Stieger and/or Dr. Fritz Blumer, Homburger Rechtsanwälte, Weinbergstraße 56/58, 8006 Zurich

versus

Gerard M. Housey
100 Haven Avenue, Apt. 7E, New York, NY 10032 **"Defendant"**

represented by E. Blum Co., Vorderberg 11, 8044 Zürich, registered as representative in the patent register

regarding **A1312**

patent law

39 According to the description of the patent sued upon (page 4, second paragraph), the method comprises "the insertion of a DNA (or cDNA) sequence encoding the protein of interest (POI) into an appropriate vector and the generation of cell lines which contain either (1) the expression vector alone ("control" cell lines) or (2) the expression vector which contains the inserted DNA (or cDNA) sequence encoding the protein of interest (POI) ("test" cell lines). Using appropriate vector systems, recipient cell lines and growth conditions, therefore, test cell lines can be generated which stably overproduce the corresponding POI. Under suitable growth conditions these cell lines show a "graded cellular response" to POI activators or inhibitors. Thus a screening system can be set up in which the control and test cell lines can be propagated under defined growth conditions on tissue culture dishes (or even in test animals) and a large number of compounds (or crude substances which may contain active compounds) can be examined for their effect on the POI."

40 *According to the invention in accordance with the patent sued upon, therefore, cells are altered by genetic methods (alteration of the genetic material) in such a way that they overproduce a specific protein (the "protein of interest", POI).* The term "overproduction" means that the POI is expressed in higher quantities in the genetically altered cells than in the cells of the original cell line (patent sued upon, enclosure 4, bottom of page 9). In addition to the "test cell line" altered with a view to the production of the POI, a "control cell line" is also observed, in which the POI is not overproduced, but which in other respects largely accords with the test cell line. According to the above quotation from the patent specification, the vector inserted in the test cell line is even inserted in the control cell line (with the difference that the vector inserted in the control cell line does not encode the POI).

41 The broad degree of identity between the test cell line and the control cell line ensures that the effect of the substances to be investigated for their inhibitor or activator characteristics can be carried out specifically for the POI, and that the results of the tests cannot be falsified by alterations to the test cell line which cannot be attributed to the effect of the substances being investigated on the POI. This high selectivity of the method in accordance with the patent sued upon is (together with the simplicity of execution) the main advance provided by the invention as compared with the state of the art (cf. section 7.2, paras. 31 ff. above on the state of the art).

7.4 The patent claims

7.4.1. The claims granted

42 Independent <u>claim 1</u>

Method of determining whether a substance is an inhibitor or an activator of a protein, whose presence in a cell evokes a responsive change in a phenotypic characteristic other than the level of said protein in saide cell per se, which comprises:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	09/510,562	Confirmation No.: 3061
Applicant	:	Gerard M. Housey	
Filed	:	February 22, 2000	
TC/A.U.	:	1636	
Examiner	:	Guzo, D.	
Docket No.	:	395/35	
Customer No.	:	23838	

Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Declaration of Dr. Gerard M. Housey Under 37 C.F.R. § 1.131

SIR:

I, Gerard M. Housey, M.D., Ph.D., hereby declare and state to the best of my knowledge, information and belief, as follows:

1. I am the inventor of the subject matter disclosed and claimed in the above-identified patent application. The present application claims priority as a continuation of U.S. Serial No. 08/917,444, filed August 22, 1997, abandoned, which is a division of U.S. Serial No. 08/408,443, filed March 17, 1995, now U.S. Patent No. 5,688,655, which is a continuation of U.S. Serial No. 07/977,986, filed November 18, 1992, abandoned, which is a continuation of U.S. Serial No. 07/392,073 filed August 10, 1989, now U.S. Patent No. 5,266,464, which is a continuation-in-part of U.S. Serial No. 07/154,206, filed February 10, 1988, now U.S Patent No. 4,980,281 ("the '281 patent").

2. I am familiar with the Office Action mailed August 8, 2003 and the reference cited therein (Riedel et al. (1987) *Science* 236(4798):197-200). Science is published weekly. The first issue of Vol. 236 (Issue 4797), bearing the issue date "3 April 1987" (Exhibit A) was

B), was received by that same library on April 13, 1987. Thus, Riedel was not available to the public earlier than April 10, 1987. I understand that the publishers of Science (The American Association for the Advancement of Science) have confirmed to my attorney that Science is published weekly, and is available to the public on the date printed on the cover, and is mailed to subscribers no earlier than that date.

3. The presently claimed invention was conceived prior to April 9, 1987. Evidence of this fact is shown in the attached Exhibit C, which is part of a research report that describes my work and bears a date prior to April 9, 1987.

4. Exhibit C reflects my conception of the subject matter recited in the pending claims, that had occurred by April 9, 1987. Figures 7 and 8 hypothesize how D- and L-amino acids would be transported into a cell if the cell contained a functional D-amino acid transport system (Figure 7) and how such a hypothetical transport system would respond to potential inhibitors or activators of the transport system (Figure 8). Taken together, Figures 7 and 8 reflect my conception that a hypothetical target protein would be able to confer upon a cell the ability to become responsive to inhibitors or activators which interact with (bind to) the target protein, and thus demonstrates my concept of a *responsive change in a phenotypic characteristic* which is capable of being evoked by the production of a protein in a cell (other than the level of the protein in the cell per se) as taught in Claim 1 and the specification of the '281 patent.

5. Reduction to practice of the claimed subject matter occurred no later than June 13, 1987. Exhibit D is a page from my laboratory notebook that describes photomicrographs that I prepared of test and control cells under various conditions. Exhibits E and F consist of photomicrographs of treated or untreated control cells or test cells. Exhibits D - F provide experimental evidence for the claimed invention.

6. In particular, Exhibit D, bearing the date "6/13/87," summarizes photomicrographs that were assembled for a symposium in which I was then planning to participate at the Banting and Best Diabetes Center in Toronto, Canada on June 19, 1987. Lines 7-21 describe photomicrographs of untreated control and test cells. Lines 22-29 describe photomicrographs of control cells and R6-PKC3 and R6-PKC5 test cells in the absence or presence of TPA, a known activator of PKC. The photomicrographs of Exhibit E are described in Exhibit D, and depict untreated test cells exhibiting the property of post-confluence foci formation. (See Specification, Fig. 6 and the description of Fig. 6 at page 8, lines 1-7; '281 patent, Col. 4, lines 21-27; Col. 9, lines 41-58). Exhibit F consists of photomicrographs of R6-C1 control cells and R6-PKC3 test cells treated with and without tamoxifen. The photomicrographs of Exhibit F were prepared at the same time as the photomicrographs of Exhibit E. Similar to lines 22-29 of Exhibit D, the photomicrographs of Exhibit F depict control and test cells which are untreated or treated with tamoxifen in the post-confluence foci formation assay. Panels A and B depict R6-C1 control cells at time 0 and 10 days later, respectively. Panels C and D depict untreated R6-PKC3 test cells at time 0 and 10 days later, respectively. Panels E and F depict tamoxifen treated R6 PKC3 test cells at time 0 and 10 days later, respectively. Although I did participate in that symposium on June 19, 1987, none of the results depicted in lines 22-29 of Exhibit D, nor any portion of Exhibits E and F, were presented.

7. The results discussed above were compiled in a series of invention reports that were provided to my attorney beginning in 1987 and continuing through February 9, 1988.

8. I exercised diligence in the completion of the invention from immediately prior to the publication of Riedel until the date of reduction to practice identified above. The focus of my work during this time was devoted to development of the claimed invention.

9. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that the undersigned acknowledges that any false statements and the like so made are punishable by fine or imprisonment or both under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of any patent that issues from U.S. Application Serial No. 09/510,562.

Date October 22, 2003

Gerard M. Housey, M.D., Ph.D.